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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/345,148	SEGAL, ANDREW H.	
	Examiner	Art Unit	
	Phillip Gambel	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 July 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-16,19-68,70 and 71* is/are pending in the application.

4a) Of the above claim(s) *15,16,25 and 30-68* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 3-14, 19-24, 26-29 and 70-71* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. As indicated in applicant's Response to the Restriction Requirement, filed 07/26/2007; applicant provisionally elected

Species B: "a cell comprises the antigen and the cell is a non-recombinant cell and wherein the engineered ligand for CD40, which comprises a ligand for CD40 and a moiety heterologous to said ligand for CD40, wherein said moiety that binds to said cell is a separate element but has been admixed with the non-recombinant cell comprising an antigen and the cell, antigen and the engineered ligand and moiety are all combined prior to administration" for continued examination, with traverse.

Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

As indicated previously, applicant has elected the following species as it reads on "methods of vaccinating a mammal to an antigen, the method comprising":
"a cell" as it reads on "a tumor cell",
"an exogenous engineered ligand for CD40" as it reads on "an anti-CD40 antibody",
"an opsonin enhanced cell" as it reads on "the alpha chain of C3b", and
"a cytokine as it reads on "IL-2".

In an effort to move the prosecution of the instant application along, the species of the "ligand for CD40" has been extended to include the "CD40L" in addition to the election of "anti-CD40 antibodies" of record.

Claims 1, 3-16, 19-68 and 70-71 are pending.

Claims 2, 17-18 and 69 have been canceled.

Claims 1, 3-14, 19-24, 26-29 and 70-71 are under consideration as they read on the elected invention and species.

Claims 15-16, 25 and 30-68 have been withdrawn from consideration as being drawn to non-elected inventions or species.

It is noted that a pathogenic cell reads on a tumor cell consistent with the disclosure on pages 9-10, overlapping paragraph of the Substitute Specification, filed 04/10/2003.
Therefore, claim 25 has been withdrawn from consideration as it reads on the elected species.

Upon a review of the recitation of claim 27 and the elected species, claim 27 is under consideration in the instant application.

Further, as indicated above, the species of the ligand for CD40 has been extended to CD40L, therefore claims 19-20 are under consideration in the instant application.

Although tumor cells can act as antigen-presenting cells, claims 15-16 remain withdrawn from consideration as the antigen-presenting cells recited in these claims appear to read on the classic or professional antigen presenting cells described on page 14, paragraph 1 of the Substitute Specification, filed 04/10/2003.

2. Upon reconsideration of applicant's arguments concerning the metes and bounds as well as the intent of the claimed invention, including applicant's election of species indicated above,
New Grounds of Rejection have been set forth herein.

3. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o).
Correction of the following is required:

The written description of "at least 30 contiguous amino acid residues of a CD154 molecule" in the specification is not readily apparent.

Applicant is required to amend the specification to provide proper antecedent basis.

Alternatively, applicant is invited to indicate written support for this limited recited in claim 19.

5. This is a rejection under 35 USC § 112, first paragraph, "written description" (and not new matter).

Claims 1, 3-14, 19-24, 26-29 and 70-71 are rejected under 35 U.S.C. § 112, first paragraph, as the specification does not contain a written description of the claimed invention, in that the disclosure does not reasonably convey to one skilled in the relevant art that the inventor(s) had possession of the claimed invention at the time the application was filed.

A) There is insufficient written description encompassing "ligand for CD40" because the relevant identifying characteristics such as structure of other physical and/or chemical characteristics of the genus of "ligand(s) for CD40" are not set forth in the specification as filed, commensurate in scope with the claimed invention.

Page 11, paragraph 3 of the Substitute Specification, filed 04/10/2003, describes the "ligand for CD40", but provides for no structure.

Further, pages 15-17 of the Substitute Specification describes the known "ligands for CD40" as either the CD40 ligand (i.e., CD40L or CD154) or anti-CD40 antibodies.

However, the instant disclosure as filed does not provide for any "ligand for CD40" other than that what was known by the skilled artisan in the art at the time the invention was made and the claims are not limited to known "ligands for CD40".

A skilled artisan cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus of "ligands for CD40" that exhibit the functional property of enhancing a cell (e.g., a tumor cell) in vaccinating a mammal to antigen, broadly encompassed by the claimed invention.

B) There is insufficient written description encompassing "at least 30 contiguous amino acid residues of a CD154 molecule" because the relevant identifying characteristics such as structure of other physical and/or chemical characteristics of the genus of "at least 30 contiguous amino acid residues of a CD154 molecule" are not set forth in the specification as filed, commensurate in scope with the claimed invention.

For example, the CD40L / CD154 is a homotrimer and not any 30 contiguous amino acids would be expected to have the property of enhancing a cell (e.g., a tumor cell) in vaccinating a mammal to antigen.

The problem here is that the instant specification fails to provide a disclosure of which "at least 30 contiguous amino acid residues" are required for the CD40L / CD154 to enhance a cell (e.g., a tumor cell) in vaccinating a mammal to antigen, broadly encompassed by the claimed invention.

A skilled artisan cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus "of at least 30 contiguous amino acid residues of a CD154 molecule" that exhibit this functional property.

C) There is insufficient written description encompassing "a cytokine consisting of a ligand for one of the following receptors as it reads on the IL-2 receptor" (see claim 8) as it reads on the elected species of "IL-2" because the relevant identifying characteristics such as structure of other physical and/or chemical characteristics of the genus of "cytokines other than IL-2" are not set forth in the specification as filed, commensurate in scope with the claimed invention.

Pages 18-22 of the Substitute Specification, filed 04/10/2003, describes the known "IL-2" and its known structures, but does not provide for cytokines other than IL-2 that are ligands for the IL-2 receptor, which can aid in vaccinating a mammal to antigen, broadly encompassed by the claimed invention.

A skilled artisan cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus "of at least 30 contiguous amino acid residues of a CD154 molecule" that exhibit this functional property of enhancing a cell (e.g., a tumor cell) in vaccinating a mammal to antigen, broadly encompassed by the claimed invention.

In addition, the following is noted as it applies to (A), (B) and (C) herein.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016.

One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481, 1483.

Thus, the specification fails to describe these DNA sequences. The Court further elaborated that generic statements are not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function. Finally, the Court indicated that while applicants are not required to disclose every species encompassed within a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, defined by nucleotide sequence, falling within the scope of the genus, See The Regents of the University of California v. Eli Lilly and Company, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997).

Applicant is relying upon certain biological activities and the disclosure of this limited representative number of species to support an entire genus. The instant invention encompasses employing any "ligand(s) for CD40", "at least 30 contiguous amino acid residues of a CD154 molecule" and/or "a cytokine consisting of a ligand for one of the following receptors as it reads on the IL-2 receptor" to aid in vaccinating a mammal, yet the instant specification does not provide sufficient written description as to the structural features of said "ligand(s) for CD40", "at least 30 contiguous amino acid residues of a CD154 molecule" and/or "a cytokine consisting of a ligand for one of the following receptors as it reads on the IL-2 receptor" as broadly encompassed by the claims.

Also, the specification does not provide for the correlation between the chemical structure and the function of the genus of "ligands for CD40", "at least 30 contiguous amino acid residues of a CD154 molecule" and/or "a cytokine consisting of a ligand for one of the following receptors as it reads on the IL-2 receptor" broadly encompassed by the claimed invention.

The reliance on the disclosed limited examples of certain known "ligands for CD40" or "IL-2" indicated above and disclosed in the specification as filed does not support the written description of any "ligand(s) for CD40, "at least 30 contiguous amino acid residues of a CD154 molecule" and/or "a cytokine consisting of a ligand for one of the following receptors as it reads on the IL-2 receptor"

The specification as filed does not provide written description for "ligands for CD40","at least 30 contiguous amino acid residues of a CD154 molecule" and/or "a cytokine consisting of a ligand for one of the following receptors as it reads on the IL-2 receptor" structurally unrelated to the limited species of the "CD40L/CD154 and anti-CD40 antibodies" or "IL-2" indicated above and disclosed in the specification as filed and encompassed by the claimed invention.

There is insufficient guidance based on the reliance on the certain known "ligands for CD40", "at least 30 contiguous amino acid residues of a CD154 molecule" and/or "a cytokine consisting of a ligand for one of the following receptors as it reads on the IL-2 receptor" indicated above and disclosed in the specification as filed to direct a person of skill in the art to select or to predict particular sequences as essential for identifying any "ligand(s) for CD40" nor what other "ligand(s) for CD40", "at least 30 contiguous amino acid residues of a CD154 molecule" and/or "a cytokine consisting of a ligand for one of the following receptors as it reads on the IL-2 receptor", are employed in the claimed methods, as encompassed by the claimed invention.

Mere idea or function is insufficient for written description; isolation and characterization at a minimum are required

The instant claims do not provide sufficient structural and functional characteristics coupled with a known or disclosed correlation between function and structure. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus of "ligand(s) for CD40", "at least 30 contiguous amino acid residues of a CD154 molecule" and/or "a cytokine consisting of a ligand for one of the following receptors as it reads on the IL-2 receptor";
the specification does not provide sufficient written description for the genus of "ligand(s) for CD40" "at least 30 contiguous amino acid residues of a CD154 molecule" and/or "a cytokine consisting of a ligand for one of the following receptors as it reads on the IL-2 receptor", broadly encompassed in the claimed methods.

The Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement make clear that if a claimed genus does not show actual reduction to practice for a representative number of species; then the Requirement may be alternatively met by reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001, see especially page 1106 column 3).

In the absence of structural characteristics that are shared by members of the genus of "ligand(s) for CD40", "at least 30 contiguous amino acid residues of a CD154 molecule" and/or "a cytokine consisting of a ligand for one of the following receptors as it reads on the IL-2 receptor" employed in the claimed methods to vaccinate mammals;
one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus.
Thus, Applicant was not in possession of the claimed genus. See University of California v. Eli Lilly and Co. 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997).

Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.
Also, see MPEP 2163.

"Adequate written description requires a precise definition, such as by structure, formula, chemical name or physical properties, not a mere wish or plan for obtaining the claimed chemical invention." Id. at 1566, 43 USPQ2d at 1404 (quoting Fiers, 984 F.2d at 1171, 25 USPQ2d at 1606). Also see Enzo-Biochem v. Gen-Probe 01-1230 (CAFC 2002).

Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115.)

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office Action:

> A person shall be entitled to a patent unless --
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

7. The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office Action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103(a).

8. Claims 1, 5-13, 19-24, 28-29 and 71 are rejected under 35 U.S.C. § 102 (e) as anticipated Selvaraj et al. (U.S. Patent No. 6,491,925) (see entire document).

Selvaraj et al. teach methods of vaccinating against tumor or tumor antigens with immunotherapeutic compositions comprising neoplastic cells or neoplastic cell membranes and GPI-costimulatory cell adhesion molecules (see entire document, including Summary of the Invention and Detailed Description of the Invention).

In addressing costimulatory cell adhesion molecules, Selvaraj et al. teach providing costimulation for enhancing various T cell responses, including anti-tumor immune responses, wherein the molecules known to enhance said responses include CD40 and its ligand (e.g., see column 14, paragraph 2; column 15, paragraph 1; and column 20, paragraph 3).

In addressing GPI-costimulatory molecules fusion proteins, Selvaraj et al. teach providing said GPI-costimulatory molecules fusion proteins and note the potential disadvantages of genetic manipulation (e.g. see column 7-8, overlapping paragraph) and the techniques to interconvert membrane isoforms by molecular biological techniques and exemplify the exogenous GPI-anchored B7-1 added to the tumor cell / membrane preparation (e.g., see columns 7-23).

It is noted that Selvaraj et al. teach that tumor cells can function as antigen-presenting cells (e.g., See the third paragraph of the Background of the Invention in column 1).

Selvaraj et al. also teach that for in vivo human immunotherapeutic purposes, live tumor cells are not appropriate and attenuated tumor cells are employed, including the use of irradiation (e.g., see column 11, paragraphs 2-4; column 19, paragraph 2; column 21, paragraphs 1 and 4).

In teachings the conditions for providing vaccine compositions, Selvaraj et al. do teach conditions that read on admixing tumor cells and GPI-costimulatory fusion proteins (see Summary of the Invention and Detailed Description of the Invention and notes that the art knows how to administer immunogenic or immunotherapeutic compositions so as to generate protective and/or therapeutic immune responses (e.g., see column 20, paragraph 4).

Although Selvaraj et al. focuses on other cytokines, this reference acknowledges that cytokines such as IL-2 have been shown to be effective in inducing anti-tumor immune responses (e.g., see column 12, paragraph 1) and does teach the use of cytokines in their immunotherapeutic compositions (e.g., see columns 2-3, overlapping paragraph; column 13, paragraph 4 – column 14, paragraph 1; column 22, paragraph 3).

Also, Selvaraj et al. teach that cytokines can be GPI-anchored as well. (e.g., see column 22, paragraph 3).

Although Selvaraj et al. teach the disadvantages of genetically modifying cells over the use of anchoring molecules of interest via GPI,
Selvaraj et al. do teach the known methods of genetically modifying cells of interest with the molecule of interest at the time the invention was made (e.g., see column 7, paragraphs 1-3; column 19, paragraph 4).
Therefore, one of ordinary skill in the art at the time the invention was made would have immediately envisaged that genetically expressing molecules of interest, including cytokines such as IL-2, in tumor cells, given the teachings of Selvaraj et al.

It does not appear that the claim language or limitations result in a manipulative difference in the method steps when compared to the prior art disclosure.
See Bristol-Myers Squibb Company v. Ben Venue Laboratories 58 USPQ2d 1508 (CAFC 2001).

It is the burden of the applicant to show the unobvious difference between the claimed and disclosed methods and compositions. Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. Also, the Courts have held that there is no requirement that those of ordinary skill in the art know of the inherent property. See MPEP 2131.01(d) and MPEP 2112 - 2113 for case law on inherency.

6. Claims 1, 5-14, 19-24, 26, 28-29 and 71 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Selvaraj et al. (U.S. Patent No. 6,491,925) in view of Grossmann et al. (Human Gene Therapy 8: 1935-1943, 1997), Kato et al. (J. Clin. Invest. 101 : 1133-1141, 1998), Hoo (U.S. Patent No. 5,891,432), Maraskovsky et al. (U.S. Patent No. 6,017,527), (Dullforce et al. (Nature Medicine 4: 88-91, 1998; 1449), Heath et al. (WO 94/04570), Heath et al. (Eur. J. Immunol., 24: 1828-1834, 1994), the well known use of engineering attachment of a lipid such as a long-chain fatty acid to a molecule such as a peptide to permit the complex to stably associated with the plasma membrane , including the use of palmitate as acknowledged on pages 64- 67 of the instant specification (see Engineered Opsonins, Cytokines or Ligands for CD40 Containing a Lipid), including the teachings of Kaplan et al. (WO 96/32140) and Caras (U.S. Patent No. 5,374,548).

Selvaraj et al. teach methods of vaccinating against tumor or tumor antigens with immunotherapeutic compositions comprising neoplastic cells or neoplastic cell membranes and GPI-costimulatory cell adhesion molecules (see entire document, including Summary of the Invention and Detailed Description of the Invention).

In addressing costimulatory cell adhesion molecules, Selvaraj et al. teach providing costimulation for enhancing various T cell responses, including anti-tumor immune responses, wherein the molecules known to enhance said responses include CD40 and its ligand (e.g., see column 14, paragraph 2; column 15, paragraph 1; and column 20, paragraph 3).

In addressing GPI-costimulatory molecules fusion proteins, Selvaraj et al. teach providing said GPI-costimulatory molecules fusion proteins and note the potential disadvantages of genetic manipulation (e.g. see column 7-8, overlapping paragraph) and the techniques to interconvert membrane isoforms by molecular biological techniques and exemplify the exogenous GPI-anchored B7-1 added to the tumor cell / membrane preparation (e.g., see columns 7-23).

It is noted that Selvaraj et al. teach that tumor cells can function as antigen-presenting cells (e.g., See the third paragraph of the Background of the Invention in column 1).

Selvaraj et al. also teach that for in vivo human immunotherapeutic purposes, live tumor cells are not appropriate and attenuated tumor cells are employed, including the use of irradiation (e.g., see column 11, paragraphs 2-4; column 19, paragraph 2; column 21, paragraphs 1 and 4).

In teachings the conditions for providing vaccine compositions, Selvaraj et al. do teach conditions that read on admixing tumor cells and GPI-costimulatory fusion proteins (see Summary of the Invention and Detailed Description of the Invention and notes that the art knows how to administer immunogenic or immunotherapeutic compositions so as to generate protective and/or therapeutic immune responses (e.g., see column 20, paragraph 4).

Although Selvaraj et al. focuses on other cytokines, this reference acknowledges that cytokines such as IL-2 have been shown to be effective in inducing anti-tumor immune responses (e.g., see column 12, paragraph 1) and does teach the use of cytokines in their immunotherapeutic compositions (e.g., see columns 2-3, overlapping paragraph; column 13, paragraph 4 – column 14, paragraph 1; column 22, paragraph 3).

Also, Selvaraj et al. teach that cytokines can be GPI-anchored as well. (e.g., see column 22, paragraph 3).

Although Selvaraj et al. teach the disadvantages of genetically modifying cells over the use of anchoring molecules of interest via GPI,
Selvaraj et al. do teach the known methods of genetically modifying cells of interest with the molecule of interest at the time the invention was made (e.g., see column 7, paragraphs 1-3; column 19, paragraph 4).

Therefore, one of ordinary skill in the art at the time the invention was made would have immediately envisaged that genetically expressing molecules of interest, including cytokines such as IL-2, in tumor cells, given the teachings of Selvaraj et al.

Although Selvaraj et al. teach GPI-costimulatory molecules fusion proteins, including CD40L/CD154 as well as CD40L-CD40-mediated enhancement of immune response,
Selvaraj et al. differs from the claimed methods by not describing the elected species of anti-CD40 antibodies as the CD40 ligand of interest.

In addition to the teachings of Selvaraj et al., Grossman et al. and Kato et al. of record teach the important role and ability of CD40L to activate immune responses, including anti-tumor responses.

Grossmann et al. teach the transgenic expression of CD40L, which acts as a costimulator, to increase immune responses, including immune responses to a weakly immunogenic tumor (see entire document, including the Abstract). Grossman et al. teach that only a few cells need to be engineered to express CD40L to produce the appropriate immune response to the antigen or cell expressing the antigen (see Discussion, including page 1941, column 2, paragraph 3).

Kato et al. teach that CD40-CD40 ligand interaction plays a critical role in immune activation and that expressing a functional ligand for CD40 on a leukemia cell induces the desired immune responses to that leukemia cell but also for unmodified targeted tumor cells (see entire document, including the Abstract). Here, leukemic B cells were infected with a replication defective adenorvirus vector encoding CD40 ligand (see entire document, including Abstract, Results and Discussion).

In addition to the teachings of providing GPI-costimulatory molecules to tumor cells and tumor cell membrane preparations to provide for antigen presentation to boost anti-tumor responses, as taught by Selvaraj et al.,

Maraskovsky et al. of record teach the methods of vaccination with antigen-expressing activated dendritic cells, including stimulating immune responses with the administration of other cytokines such as the CD40 ligand and IL-2 (see entire document, including column 6, paragraph 1; column 11, paragraph 4). Here, transfecting the dendritic cells to express the cytokines is also taught.

Maraskovsky et al. teach antigens from a number of pathogenic organisms encompassed by the claimed invention, including bacteria, virus tumor associated antigens (see Preparation of Antigens on columns 10-11).

In addition to the teachings of Selvaraj et al. and Maraskovsky et al. concerning the use of IL-2 in immunotherapeutic compositions to treat tumors,

Hoo et al. clearly teach the use of IL-2 in immunotherapeutic compositions and modalities in the treatment of cancer (see entire document, including the Detailed Description of the Invention).

Also, it is noted that Hoo et al. is consistent with the teachings above in the use of a CD40 or CD40 ligand in vaccines (e.g., see columns 18-19, overlapping paragraph).

In addition to the teachings of Selvaraj et al. as to the applicability of mediating anti-tumor responses via the CD40-CD40L pathway,

The following of record also teach the ability of anti-CD40 antibodies in augmenting immune responses, including anti-tumor responses of interest.

It is noted that Maraskovsky et al. teach that anti-CD40 antibodies have been shown to mediate various biological activities (see column 7, lines 61-65).

It is noted Maraskovsky et al. differs from the claimed methods by not disclosing the administration of agonistic CD40-specific antibodies per se.

Dullforce et al. teach the administration of agonistic CD40-specific antibodies as adjuvants to stimulate B cells and antigen presenting cells against bacterial pathogens (see entire document, including Abstract).

While Dullforce et al. focus on T cell-independent immune responses, it would have been obvious to one of ordinary skill in the art at the time the invention was made that the administration of known agonistic anti-CD40 antibodies would have been applicable to various pathogenic organisms and antigens. It is noted that anti-CD40 antibodies stimulate antigen presenting cells and that human B cells are antigen presenting cells.

Heath et al. (Eur. J. Immunol., 1994) teach anti-CD40 antibodies, including various epitopic specificities, that are capable of stimulating immune responses such as B cells as well as the use of such antibodies in infectious diseases and malignancy (page 1833, column 2) (see entire document, including Abstract and Discussion).

Heath et al. (WO 94/0570) teach treating $CD40^-$ malignancies by making such $CD40^-$ malignancies express CD40 by transformation or liposome fusion, which leads to stimulating T cells and promoting the desired immune response (see entire document, including pages 24-25, overlapping paragraph). Although Heath et al. is describing making a cell $CD40^+$, Heath et al. is clear that liposomes can serve to target to particular tissues or cells displaying the CD40 molecule or its ligand (e.g. see page 23, paragraph 4).

Therefore, the prior art provides for expressing CD40L or anti-CD40 antibodies with or on cells to stimulate desired immune responses to antigens of interest. While these references provide for various means to engineer the cells to express said immunostimulatory CD40L or anti-CD40, these references do not provide explicit teachings of the well known use of engineering a desired molecule for cell expression by engineering said desired molecule with a heterologous cell membrane binding moiety.

Pages 64- 67 of the instant specification (see Engineered Opsonins, Cytokines or Ligands for CD40 Containing a Lipid) provide for a number of teachings that acknowledge the well known use of engineering attachment of a lipid such as a long-chain fatty acid to a molecule such as a peptide to permit the complex to stably associated with the plasma membrane, including the use of palmitate.

With respect to the use of GPI-anchored molecules as it reads on antibodies, particularly anti-CD40 antibodies; the following is noted.

Both Kaplan (see entire document, including pages 7—9, pages 14-15 and pages 24-25)

and Caras (see entire document, including column 3, paragraph 4 to column 4, paragraph 2; columns 7-8, overlapping paragraph) teach the use of GPI in anchoring antibodies or immunoglobulins.

Further, Kaplan et al. teach the applicability of the recombinant and GPI anchoring to other molecules such as cytokines at the time the invention was made (see entire document, including pages 24-25, page 27,paragraph 2).

It is noted that Caras teaches the advantages of GPI-linked polypeptides in overcoming the defects or deficiencies within the immune system in the process of antigen presentation (e.g., see column 10, paragraph 2).

Kaplan also teach palmitolyation as an example of lipid modification of protein transfer, that is, the external application of a cell surface-associating or soluble protein (e.g., see pages 6-7, overlapping paragraph).

Given that co-stimulatory nature of the CD40:CD40 ligand pathway and the co-stimulatory signal provided by anti-CD40 antibodies, the teachings of McHugh et al. are particularly relevant to the instant invention.

Given the teachings and advantages of combining co-stimulatory molecules via alternative methods as taught by the above-mentioned references, one of ordinary skill in the art at the time the invention was made would have been motivated to modify cells of interest (e.g. cells comprising a selected antigen of interest) with GPI anchored agonistic antibodies to increase stimulation to pathogenic organisms.

Therefore, one of ordinary skill in the art would have been motivated to select agonistic CD40 antibodies to stimulate immune responses via CD40:CD40 ligand interactions by expressing anti-CD40 antibody on said cells by a variety of engineering protocols, including the known use of heterologous cell membrane binding moieties via GPI or palmitoylation, as taught by Selvaraj et al. and Kaplan et al. and acknowledged on pages 64-67 of the instant specification in order to stimulate and increase desired immune response to antigens of interest, including cells expressing tumor antigens or antigens from a variety of pathogenic organisms, including tumor antigens expressed on tumor cells.

In addition to the teachings of agonistic CD40-specific antibodies, taught by Maraskovsky et al., Dullforce et al., Heath et al. (Eur. J. Immunol.), and Heath et al. (WO), it was well known and practiced at the time the invention was made to generate recombinant antibodies such as chimeric antibodies, humanized antibodies and fragments thereof to decrease immunogenicity and increase half-life of such recombinant antibodies. Such anti-CD40 antibodies would comprise the idiotypic portion of an antibody which binds CD40. Given the well known use and practice of recombinant technology to produce homogeneous proteins at the time the invention was made, engineered CD40-specific antibodies as well as engineered cytokines encompassed by the claimed invention would have been obvious to one of ordinary skill in the art at the time the invention was made.

The patentability of a product does not depend on its method of production. In re Thorpe, 227 USPQ 964, 966 (Fed. Cir. 1985). See MPEP 2113.

Further, given the teachings of Selvaraj et al., Maraskovsky et al. of vaccinating for tumor antigens, including the use of CD40:CD40 ligand pathway and IL-2 (see above) and the teachings of Selvaraj et al. and the secondary references above for teaching the provision of co-stimulatory signals in conjunction with tumor cell vaccination, the ordinary artisan would have been motivated at the time the invention was made to combine the co-stimulatory signal of anti-CD40 antibodies, taught by Dullforce et al., Caux and Heath, in conjunction with the tumor cells themselves to vaccinate against tumor cells and/or antigens of interest. It would have been immediately apparent to one of ordinary skill in the art that tumor cells would have been attentuated so that tumor cells would not be able to divide and proliferate in a host, as taught by Selvaraj et al. If not, the tumor cells could proliferate to the point of being detrimental to the subject of the vaccination.

From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

"The test of obviousness is not express suggestion of the claimed invention in any or all of the references but rather what the references taken collectively would suggest to those of ordinary skill in the art presumed to be familiar with them." See In re Rosselet, 146 USPQ 183, 186 (CCPA 1965).

"There is no requirement (under 35 USC 103(a)) that the prior art contain an express suggestion to combine known elements to achieve the claimed invention. Rather, the suggestion to combine may come from the prior art, as filtered through the knowledge of one skilled in the art." Motorola, Inc. v. Interdigital Tech. Corp., 43 USPQ2d 1481, 1489 (Fed. Cir. 1997).

An obviousness determination is not the result of a rigid formula disassociated from the consideration of the facts of a case. Indeed, the common sense of those skilled in the art demonstrates why some combinations would have been obvious where others would not. See KSR Int'l Co. v. Teleflex Inc., 82 USPQ2d 1385 (U.S. 2007) ("The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results.").

The motivation to combine can arise from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combine for their common known purpose, which is increasing immunogenicity in methods of vaccination in the instant case. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

8. No claim is allowed.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (571) 272-0844. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841.

The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Phillip Gambel, Ph.D., J.D.
Primary Examiner
Technology Center 1600
October 29, 2007

7. Claims 3, 4, 27 and 70 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Selvaraj et al. (U.S. Patent No. 6,491,925) in view of Grossmann et al. (Human Gene Therapy 8: 1935-1943, 1997), Kato et al. (J. Clin. Invest. 101 : 1133-1141, 1998), Hoo (U.S. Patent No. 5,891,432), Maraskovsky et al. (U.S. Patent No. 6,017,527), (Dullforce et al. (Nature Medicine 4: 88-91, 1998; 1449), Heath et al. (WO 94/04570), Heath et al. (Eur. J. Immunol., 24: 1828-1834, 1994), the well known use of engineering attachment of a lipid such as a long-chain fatty acid to a molecule such as a peptide to permit the complex to stably associated with the plasma membrane , including the use of palmitate as acknowledged on pages 64- 67 of the instant specification (see Engineered Opsonins, Cytokines or Ligands for CD40 Containing a Lipid), including the teachings of Kaplan et al. (WO 96/32140) and Caras (U.S. Patent No. 5,374,548)
as applied to claims 1, 5-14, 19-24, 26, 28-29 and 71 above
and in further view of Jacquier-Sarlin et al. (Immunology 84: 164-170, 1995).

The prior art teachings above differ from the claimed methods by not describing opsonin-enhanced cells for vaccination.

While it is noted that claims 3, 4 27 and 70 do not necessarily require all of the elements set forth in claims 1, 5-14, 19-24, 26, 28-29 and 71 above;
given the comprising language and in the interest of compact prosecution,
This rejection addressing the opsonin-enhanced cells for vaccination have been set in this manner accordingly.

Jacquier-Sarlin et al. teach the use of complement fragments including C3b to enhance immune responses to antigens of interest (see entire document). By increasing antigen processing and presentation, C3b could be engineered into new vaccines (see Discussion, particularly the last paragraph on page 169).

Given the teachings of Jacquier-Sarlin et al. that C3b which would include the alpha chain of C3b, increases antigen processing and presentation which would be useful for engineering vaccines, one of ordinary skill in the art would have been motivated to incorporate C3b into vaccine preparations to a host of pathogenic organisms and antigens, including tumor antigens in order to increase immunogenicity and, in turn, increase immune responses to antigens of interest.

Therefore, it would have obvious to a person of ordinary skill in the art at the time the invention was made to apply the teachings of Jacquier-Sarlin to incorporate C3b into the methods of vaccination via alternative modes of compositions comprising immunogenic cells, anti-CD40 antibodies and IL-2, as taught above to obtain vaccination by a highly immunogenic composition to pathogenic organisms of interest, including tumor cells.